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APPLICATION NUMBER: 60/534,205

FILING DATE: *January 05, 2004*

RELATED PCT APPLICATION NUMBER: PCT/US04/37793

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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 C.F.R. 1.53 (c).

17681	Docket Number	235.0054 0161		Type a plus sign (+) inside this box >	+
US PTO	INVENTOR(s)/APPLICANT(s)				
	Name (last, first, middle initial)		RESIDENCE (CITY, AND EITHER STATE OR FOREIGN COUNTRY)		
	Ferguson, Duncan C.		Bogart, Georgia		
19587 60/534205	TITLE OF THE INVENTION (280 characters max)				
DNA SEQUENCE AND EXPRESSED RECOMBINANT GLYCOPROTEINS RELATED TO FELINE THYROTROPIN (TSH)					
CORRESPONDENCE ADDRESS					
Mueting, Raasch & Gebhardt, P.A. P.O. Box 581415 Minneapolis					
Attn: Victoria A. Sandberg					
STATE	Minnesota	ZIP CODE	55458-1415	COUNTRY	United States of America
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/>	Specification	Number of Pages	10	Small Entity Statement	
<input type="checkbox"/>	Drawing(s)	Number of Sheets		Other (specify)	
METHOD OF PAYMENT (check one)					
<input checked="" type="checkbox"/>	A check or money order is enclosed to cover the Provisional filing fees			PROVISIONAL FILING FEE AMOUNT	(\$) 160.00
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government:
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Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,
SIGNATURE Victoria A. Sandberg

TYPED OR PRINTED NAME Victoria A. Sandberg

Date Jan 5, 2004
REGISTRATION NO. 41,287

Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

010504

Applicant(s):

Duncan C. Ferguson

Docket No.:

235.0054 0161

Title: DNA SEQUENCE AND EXPRESSED RECOMBINANT GLYCOPROTEINS RELATED TO FELINE THYROTROPIN (TSH)

Assistant Commissioner for Patents

MAIL STOP: PROVISIONAL APPLICATION

P.O. Box 1450

Alexandria, VA 22313-1450

We are transmitting the following documents along with this Transmittal Sheet (which is submitted in triplicate):

 PROVISIONAL PATENT APPLICATION including:

Specification (10 consecutively numbered pgs, including 0 claims);
 Drawings (figures on sheets);
 Photographs (sheets);
 Provisional Application Cover Sheet (1 pg).
 A check in the amount of \$ 160.00 to pay the provisional application filing fee.
 Verified statement(s) establishing small entity status of this application under 37 C.F.R. 1.9 and 1.27 is/are enclosed.
 An itemized return postcard.
 An Assignment of the invention to _____ and Recordation Form Cover Sheet (pgs).
 A check in the amount of \$40.00 to cover the Assignment Recording Fee.
 Computer readable form of "Sequence Listing." Applicants state that the paper copy form of the "Sequence Listing" section of the present application, and the computer readable form submitted herewith, are the same.
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By: 
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By: Sandy Truehart
 Name: Sandy Truehart

(PROVISIONAL TRANSMITTAL UNDER RULE 1.10)

**DNA SEQUENCE AND EXPRESSED RECOMBINANT GLYCOPROTEINS RELATED TO
FELINE THYROTROPIN (TSH)**

A United States Provisional Patent Application

DNA SEQUENCE AND EXPRESSED RECOMBINANT GLYCOPROTEINS RELATED TO FELINE THYROTROPIN (TSH)

ABSTRACT

Newly established sequence and DNA constructs of the alpha and beta subunits of the pituitary glycoprotein thyrotropin (TSH) of the cat, and a new process to express the glycoproteins in high quantity. Constructs include a sequence for individually expressing the alpha subunit (including signal sequence and FLAG affinity tag with a Factor Xa cleavage site. The beta subunit DNA also includes intron 1 to enhance expression in mammalian cells. Another recombinant engineered "yoked" peptide engineered is a single-chain DNA sequence which encodes the alpha subunit and the beta subunit (including the first intron) linked by the C-terminal peptide of human chorionic gonadotropin. When expressed in mammalian cells (human embryonic kidney cells), this "yoked" glycoprotein is bioactive.

TECHNOLOGY DESCRIPTION

Our laboratory is the first to discover the cDNA sequence of pituitary feline alpha subunit. A report of tiger alpha subunit cDNA is 97.8% similar but not identical. Projected amino acid sequence of the 24 amino acid signal sequence and 96 amino acid alpha subunit differs from that of the tiger by 3 amino acids (97.5% homology). In addition, our feline alpha construct includes 98 additional upstream bases which we amplified from feline pituitary RNA.

We believe that the enhanced *in vivo* expression levels of the construct not only make it unique to the cat, but also an improved expression construct.

The report of the beta subunit genomic DNA structure including expressed sequence as well as the first intron has not been previously reported. The use of the cDNA for human chorionic gonadotropin (HCG) C-terminal peptide (xx amino acids) to link the alpha and beta subunits has been a strategy used previously in other laboratories and also in our laboratory for canine TSH. However, the application to the new sequence of feline TSH is novel. Please see attached sequence information for available recombinant constructs.

We are currently evaluating monoclonal antibodies developed against ovine and canine TSH for crossreactivity to feline TSH. Our next phase of research will confirm whether these monoclonal antibody pairs can detect feline TSH in a sensitive "sandwich" assay. If sensitivity is inadequate, we are preparing a monoclonal antibody later this month against the feline alpha subunit which will be paired with our 14H9.E4 beta subunit specific monoclonal antibody which we have already shown will detect heterodimeric and yoked feline TSH. We believe that the final demonstration of the fact that these recombinant standards can be used for immunoassay standards will strengthen their commercial value. We have preliminary evidence with crude proteins supporting this value but will soon do additional studies of it. Demonstration of *in vitro* (cell culture and adenylate cyclase stimulation) and *in vivo* bioactivity (increase in serum thyroid hormone concentrations and increased radioiodide uptake in cats) will serve as proof of bioactivity of the expressed constructs.

Vectors and cells – pEAK10™ expression vector and pEAK™ cells (modified HEK cells) from Edge Biosystems, 19208 Orbit Drive, Gaithersburg, MD 20879-4149

No transfer agreement – this vector was used to transfect the mammalian pEAK cells (modified Human Embryonic Kidney (HEK) cells for transient expression of alpha and beta subunits of feline TSH (TSH alpha/beta), the expression of feline alpha subunit alone, and the yoked feline TSH construct. Using puromycin selection, the line fTSHalpha /pEAK line and yfTSH/pEAK cell lines were created in our laboratory

APPLICATIONS OF THE TECHNOLOGY

1. Expression of recombinant feline thyrotropin and its subunits as immunoassay standards and immunogens for improved immunoassays against feline TSH. Such assays, particularly if sensitive enough to detect TSH suppression, would be a valuable diagnostic tool for the diagnosis of feline hyperthyroidism. A less sensitive assay would still be able to allow veterinary practitioners to monitor success of treatment with antithyroid drugs.
2. Recombinant heterodimeric or yoked feline TSH as a species-specific bioactive stimulus of thyroid function. Used as a thyroid radiosensitizing agent to increase the efficacy of a radioiodide ablative dose in thyroid adenomas and particularly in nonfunctional carcinomas. Because the structure is identical in thyrotropin, follicle stimulating hormone (FSH) and luteinizing hormone (LH), the alpha subunit can be used also to develop the subunit for combination with different beta subunits of those pituitary glycoproteins
3. Development of permanent cell lines to express feline alpha subunit – already accomplished – cell line fTSHalpha /pEAK line – the commercial value resides in the ability to independently produce the feline pituitary alpha subunit common to feline FSH, LH and TSH.
4. Development of permanent cell lines which express the yoked feline TSH construct – already accomplished – cell line yfTSH/pEAK line – the commercial value resides in the ability to produce a bioactive and immunoreactive glycosylated single-chain feline TSH.

REFERENCES

1. Genbank AF354939. *Panthera tigris* a...[gi:13561973] Baldwin,D.M., Bedows,E., Miller-Lindholm,A.K., Sherman,G.B. and Wilken,J.A. Characterization of recombinant tiger gonadotropins; Unpublished
2. Genbank AF354939. *Panthera tigris* a...[gi:13561973] Baldwin,D.M., Miller-Lindholm,A.K., Wilken,J.A., Sherman,G.B. and Bedows,E.; unpublished; Submitted (20-FEB-2001) Eppley Institute/Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, 986805 Nebraska Medical Center, Omaha, NE 68198-6805, USA
3. Genbank, AF408393. *Panthera tigris* a...[gi:22535904], Liao,M.J., Zhu,M.Y. and Zhang,A.J. *Panthera tigris altaica* pituitary glycoprotein hormone alpha subunit. Unpublished; Submitted (08-AUG-2001) College of Life Sciences, Zhejiang University, Wenshan Road 232, Hangzhou, Zhejiang 310012, China
4. Genbank AF354939. *Panthera tigris* a...[gi:13561973] Crichton,E.G., Bedows,E., Miller-Lindholm,A.K., Baldwin,D.M., Armstrong,D.L., Graham,L.H., Ford,J.J., Gjorret,J.O., Hyttel,P., Pope,C.E., Vajta,G. and Loskutoff,N.M. Efficacy of Porcine Gonadotropins for Repeated Stimulation of Ovarian Activity for Oocyte Retrieval and In Vitro Embryo Production and Cryopreservation in Siberian Tigers (*Panthera tigris altaica*) *Biol. Reprod.* 68 (1), 105-113 (2003)

SEQUENCE INFORMATION

A. Construct of Feline Thyrotropin-beta Subunit with First Intron

1 30
 5'(GAA TTC)ATG ACT GCT ATC TAC CTG ATG TCC GTG CTT
 met thr ala ile tyr leu met ser val leu
 31 75
 TTT GGC CTG GCA TGT GGA CAA GCG ATG TCT TTT TGT TTT CCA ACT
 phe gly leu ala cys gly gln ala met ser phe cys phe pro thr
 76 120
 GAG TAT ATG ATG CAT GTC GAA AGG AAA GAG TGT GCT TAT TGC CTA
 glu cys met met his val glu arg lys glu cys ala tyr cys leu
 121 162
 ACC ATC AAC ACC ACC ATC TGT GCT GGA TAT TGT ATG ACA CGG
 thr ile asn thr thr ile cys ala gly tyr cys met thr arg
Intron 1
 163 GTATGTAGTTCATCTCACTCTTTAGCTGAAAATTAGATAAACCTAGACT
 CAGTCCATTCTATCCAGAAAGGAAATGAGATAAAATCACAAACCTCATTCACAG
 ACCTAACGGTCATTGGCTCCTAGAGGTAGAGTCCCTAGGTTATAATATAACGGA
 CCTACTCCATACAGTTGGTACAGATAATTAACTACAGTTACTCCAAAGTT
 TATTTAAACCTTATCTTGTCTCTATAGGATTCAAGGATAAAAGAGAGGGTGTGTGT
 ATGTCACTTTTTTTGTCTCTATAGGATTCAAGGATAAAAGAGAGGGTGTGTGT
 GGGGAATGGGACTAAGGAATCCTCCCCAGTCCTATTGTATCTATGGGATGT
 AAGCGAATTAAACATTGCTTCCCTTCTGTGCTTCCCTCAG 580 625
 581 GAT ATC AAT GGC AAA CTG TTT CTT CCC AAA TAT GCT CTG TCC CAA
 asp ile asn gly lys leu phe leu pro lys tyr ala leu ser gln
 626 670
 GAT GTT TGC ACC TAC AGA GAC TTC CTG TAC AAG ACT GTA GAA ATA
 asp val cys thr tyr arg asp phe leu tyr lys thr val glu ile
 671 715
 CCA GGA TGC CCA CAC CAT GTT ACT CCC TAT TTC TCC TAC CCG GTA
 pro gly cys pro his his val thr pro tyr phe ser tyr pro val
 716 760
 GCT GTA AGC TGT AAA TGT GGC AAG TGT AAT ACT GAC TAT AGC GAC
 ala val ser cys lys cys gly lys cys asn thr asp tyr ser asp
 761 805
 TGC ATA CAT GAG GCC ATC AAG ACA AAT GAT TGT ACC AAA CCC CAG
 cys ile his glu ala ile lys thr asn asp cys thr lys pro gln
 806 835
 AAG TCC GAT GTG GTA GGA GTT TCT ATC TAA (GCGGCCGC₍₄₎)(AT)₅.3'
 lys ser asp val val gly val ser ile stop

() denotes the Eco RI restriction sites

Bold denotes signal sequence

Bold/italic denotes the intron 1 sequence

B. Feline Alpha Subunit Construct

(GAATTC) GCCCTT

1

45

AGT TAC TGA GAA ATC ACA AGA CGA AGC CAA AAT CCC TCT TCA GAT

ser tyr OPA glu ile thr arg arg ser gln asn pro ser ser asp

46

90

CCA CGG TCA ACT GCC CTG ATC ACA TCC TGC AAA AAG TCC GGA GGA

pro arg ser thr ala leu ile thr ser cys lys lys ser gly gly

91

135

AGG AGA GCC ATG GAT TAC TAC AGA AAA TAT GCA GCT GTC ATT CTG

arg arg ala met asp tyr tyr arg lys tyr ala ala val ile leu

136

180

GCC ATA CTC TCT GTG TTT CTG CAT ATT CTC CAT TCT TTT CCT GAT

ala ile leu ser val phe leu his ile leu his ser phe pro asp

181

225

GGA GAG TTT ACA ATG CAG GGG TGC CCA GAA TGC AAG CTA AAG GAA

gly glu phe thr met gln gly cys pro glu cys lys leu lys glu

226

270

AAC AAA TAC TTC TCC AAG TTG GGT GCC CCA ATT TAT CAA TGC ATG

Asn lys tyr phe ser lys leu gly ala pro ile tyr gln cys met

271

315

GGC TGC TGC TTC TCC AGA GCA TAC CCC ACT CCA GCA AGG TCC AAG

gly cys cys phe ser arg ala tyr pro thr pro ala arg ser lys

316

360

AAG ACA ATG TTG GTC CCA AAG AAC ATC ACC TCA GAA GCC ACA TGC

lys thr met leu val pro lys asn ile thr ser glu ala thr cys

361

405

TGT GTG GCC AAA GCC TTT ACC AAG GCC ACG GTA ATG GGA AAT GCC

cys val ala lys ala phe thr lys ala thr val met gly asn ala

Continued on next page

406

AAA GTG GAG AAT CAC ACA GAG TGC CAC TGC AGC ACT TGC TAT CAC

lys val glu asn his thr glu cys his cys ser thr cys tyr his

451 459

450

492

CAC AAG ATT (ATC GAA GGT CGT₍₁₎)(GAC TAC AAG GAC GAT GAC GAT

his lys ile ile glu gly arg asp tyr lys asp asp asp asp

493 495 510

AAG₍₂₎ (TAA₍₃₎) (GCGGCCGC₍₄₎)(TATG)₅ 3'

lys

Bold denotes 24 amino acid unexpressed signal sequence as per structure in other species

Bold italics denotes sequence upstream from expressed but not secreted signal sequence; only reported in equine; whether it is expressed is not clear.

() denotes Eco R1 restriction site from TOPO Blunt vector

Underlined denotes additional sequence from TOPO Blunt vector

((1)) denotes Factor XA site

((2)) denotes Flag tag

((3)) denotes stop codon

((4)) denotes Not1 restriction enzyme site

()₅ denotes extra bases needed for restriction enzyme to work

C. Yoked Feline TSH

1 30
5'(GAA TTC)ATG ACT GCT ATC TAC CTG ATG TCC GTG CTT
met thr ala ile tyr leu met ser val leu
31 75
TTT GGC CTG GCA TGT GGA CAA GCG ATG TCT TTT TGT TTT CCA ACT
phe gly leu ala cys gly gln ala met ser phe cys phe pro thr
76 120
GAG TAT ATG ATG CAT GTC GAA AGG AAA GAG TGT GCT TAT TGC CTA
glu cys met met his val glu arg lys glu cys ala tyr cys leu
121 162
ACC ATC AAC ACC ACC ATC TGT GCT GGA TAT TGT ATG ACA CGG
thr ile asn thr thr ile cys ala gly tyr cys met thr arg
Intron 1
163 GTATGTAGTTCATCTCACTTCTTTAGCTGAAAATTAGATAAACCTAGACT
CAGTCCATTCTATCCAGAAAGGAAATGAGATAAAATCACAACCTCATTACAG
ACCTAACGGTCATTGGCTCCTTAGAGGTAGAGTCCCTAGGTTATAATACGGA
CCTACTCCATACAGTTGGTACAGATAATTAACTAGTTTACTCCAAAGTT
TATTTAAACCTTATCTTGTCCCACGATCAAGGATAAAAGAGAGGGTGTGTGT
ATGTCATTTCCTGTCTATAGGATTCAAGTGTGGATATGCTGAATTGGTATT
GGGGAATGGGACTAAGGAATCCTCCCCAGTCCTATTGTATCTATGGGATGT
AAGCGAATTAACATTGCTTCCCTCTGTGCTTCCCTCAG 580
581 625
GAT ATC AAT GGC AAA CTG TTT CTT CCC AAA TAT GCT CTG TCC CAA
asp ile asn gly lys leu phe leu pro lys tyr ala leu ser gln
626 670
GAT GTT TGC ACC TAC AGA GAC TTC CTG TAC AAG ACT GTA GAA ATA
asp val cys thr tyr arg asp phe leu tyr lys thr val glu ile
671 715
CCA GGA TGC CCA CAC CAT GTT ACT CCC TAT TTC TCC TAC CCG GTA
pro gly cys pro his his val thr pro tyr phe ser tyr pro val
716 760
GCT GTA AGC TGT AAA TGT GGC AAG TGT AAT ACT GAC TAT AGC GAC
ala val ser cys lys cys gly lys cys asn thr asp tyr ser asp
761 805
TGC ATA CAT GAG GCC ATC AAG ACA AAT GAT TGT ACC AAA CCC CAG
cys ile his glu ala ile lys thr asn asp cys thr lys pro gln
806 beta specific primer sequence * 850
AAG TCC GAT GTG GTA GGA GTT TCT ATC CTP linker CAG GAC TCC TCT TCC TCA
lys ser asp val val gly val ser ile gln asp ser ser ser ser
851 CTP linker (continued) 892
AAG GCC CCT TCC GCC AGC CTT CCA AGC CCA ACG CGT CTC CCG
lys ala pro ser ala ser leu pro ser pro thr arg leu pro

Continued on next page

Afl III ligation site

* reverse complement in construct

893 CTP linker (continued)

alpha-
specific primer sequence
937

GGG CCC TCG GAC ACC CCG ATC CTC CCA CAA | TTT CCT GAT GGA GAG
gly pro ser asp thr pro ile ile pro gln phe pro asp gly glu

938

977

TTT ACA ATG CAG GGG TGC CCA GAA TGC AAG CTA AAG GAA
phe thr met gln gly cys pro glu cys lys leu lys glu

978

1022

AAC AAA TAC TTC TCC AAG TTG GGT GCC CCA ATT TAT CAA TGC ATG
Asn lys tyr phe ser lys leu gly ala pro ile tyr gln cys met
1023 1067

GGC TGC TGC TTC TCC AGA GCA TAC CCC ACT CCA GCA AGG TCC AAG
gly cys cys phe ser arg ala tyr pro thr pro ala arg ser lys

1068

1112

AAG ACA ATG TTG GTC CCA AAG AAC ATC ACC TCA GAA GCC ACA TGC
lys thr met leu val pro lys asn ile thr ser glu ala thr cys
1113 1157

TGT GTG GCC AAA GCC TTT ACC AAG GCC ACG GTA ATG GGA AAT GCC
cys val ala lys ala phe thr lys ala thr val met gly asn ala
1158 1202

AAA GTG GAG AAT CAC ACA GAG TGC CAC TGC AGC ACT TGC TAT CAC
lys val glu asn his thr glu cys his cys ser thr cys tyr his
1203 1211

CAC AAG ATT (ATC GAA GGT CGT₍₁₎)(GAC TAC AAG GAC GAT GAC GAT
his lys ile ile glu gly arg asp tyr lys asp asp asp asp
1245 1247 1262

AAG₍₂₎ (TAA₍₃₎) (GCGGCCGC₍₄₎)(TATG)₅ 3'
lys

* as written

Continued on next page

KEY

() denotes the Eco RI restriction sites

Bold denotes signal sequence

Bold italics denotes intron 1 sequence 1=Factor XA site

(₁) denotes Factor XA site

(₂) denotes Flag tag

(₃) denotes stop codon

(₄) denotes Not1 restriction enzyme site

()₅ denotes extra bases needed for restriction enzyme to work

The present invention is illustrated by the preceding examples. It is to be understood that the particular examples, materials, amounts, and procedures are to be interpreted broadly in accordance with the scope and spirit of the invention as set forth herein. The foregoing description and examples have been given for clarity of understanding only. No unnecessary limitations are to be understood therefrom. The invention is not limited to the exact details shown and described, for variations obvious to one skilled in the art will be included within the invention described herein.

The complete disclosure of all patents, patent applications, and publications, and electronically available material (including, for example, nucleotide sequence submissions in, e.g., GenBank and RefSeq, and amino acid sequence submissions in, e.g., SwissProt, PIR, PRF, PDB, and translations from annotated coding regions in GenBank and RefSeq) cited herein are incorporated by reference.

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By: Sandy Truehart
Name: Sandy Truehart

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